A STUDY OF SOME ESTERS OF THIOLBENZOIC ACID

A THESIS

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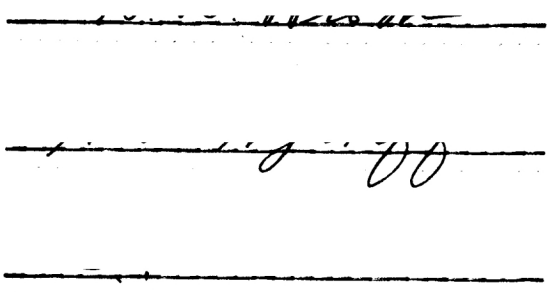
APPROVED



FOREWORD

Thiolbenzoic acid has been known for a number of years, having been synthesized as early as 1868. In spite of this fact the literature relating to the acid and compounds derived from it has been by no means extensive, and it appears to have received little attention at the hands of investigators since 1910. Certain problems presented by thiolbenzoic acid and its derivatives have, therefore, been the subject of recent research in this laboratory. Thus far, studies on the preparation of the acid and of certain of its salts and esters have been carried out, and much of the earlier literature has been checked. The present work is an extension of that which directly precedes, and had for its object the preparation and study of some of the higher esters of thiolbenzoic acid not previously reported, for the purpose of enlarging upon the knowledge of this class of compounds.

A STUDY OF SOME ESTERS OF THIOLBENZOIC ACID

Historical:

Esters of thiol acids in general may be prepared by the action of magnesium bromo mercaptide, RSMgBr, on the acid chloride or anhydride (1), and this method was used by Hepworth and Clapham (2) in preparing ethyl thiolbenzoate. Numerous other methods have been used in the preparation of esters of thiolbenzoic acid. Obermeyer (3) employed the reaction of benzoyl chloride on lead methyl mercaptide, $Pb(SCH_3)_2$, to obtain methyl thiolbenzoate, and the same type reaction was used by Tuttschieff (4) for the ethyl ester. Ethyl thiolbenzoate was also prepared by Seifert (5) from the reaction of phenyl benzoate with sodium ethyl mercaptide. Wheeler (6) obtained propyl thiolbenzoate from the action of the acid itself with benziminopropyl ether, and Engelhardt and his coworkers (7) reported a quantitative yield of isoamyl thiolbenzoate from benzoyl chloride and isoamyl mercaptan. The most convenient method, however, is that used by Wheeler (8),

(1) Taboury, Ann. Chim. Phys., 15, 5 - 66.
(2) Hepworth and Clapham, J.C.S. 119, 1188-98, (1921).
(3) Obermeyer, Ber., 20, 2922 (1887).
(4) Tuttschieff, Jahresbericht über die Fortschritte der Chemie, (1863), 484.
(5) Seifert, J. prakt. Chem., (2) 31, 471 (1885).
(6) Wheeler, J. Am. Chem. Soc., 23, 446, 448 (1901).
(7) Engelhardt, Latschinoff and Malyschieff, Zeitschrift für Chemie, (1868), 353-9.
(8) Wheeler, Am. Chem. J., 24, 69 (1900).

which employs the well known reaction between the sodium salt of the acid and the alkyl halide:

$$RCOSNa + R'X = RCOSR' + NaX \qquad (I)$$

It was by this reaction that Kimball and Reid (9) prepared the isomeric butyl thiolbenzoates, and by which Holder (10) obtained the allyl and benzyl esters.

Since the preparation of esters above isoamyl in the series has not been reported, it was thought that it might be of interest to prepare certain of the higher esters and observe their properties. Consequently, the synthesis of hexyl, heptyl, lauryl and myristyl thiolbenzoate was undertaken, using the reaction of sodium thiolbenzoate with the alkyl halide in alcoholic solution.

(9) Kimball and Reid, J. Am. Chem. Soc., 38, 2758 (1916).
(10) Holder, (Unpublished Thesis), Georgia School of Technology, 1938.

EXPERIMENTAL

PREPARATION OF SODIUM THIOLBENZOATE

The sodium salt of thiolbenzoic acid was prepared by the method recommended by Calaway (11) using the reaction of benzoyl chloride with sodium sulfide dissolved in a water-acetone mixture, followed by acidification and extraction with alkali. Thirty-five grams of hydrated sodium sulfide ($Na_2S \cdot 9H_2O$) were dissolved in 150 cc. of water, and 200 cc. of acetone added with vigorous stirring to prevent separation into two layers. Fourteen grams of benzoyl chloride were then added, forming the sodium salt of the acid:

$$C_6H_5COCl + Na_2S = C_6H_5COSNa + NaCl \qquad (II)$$

Acidification with hydrochloric acid liberated hydrogen sulfide from the excess sodium sulfide, and produced the acid:

$$C_6H_5C\ OSNa + HCl = C_6H_5COSH + NaCl \qquad (III)$$

The acid was partially separated from solution by dilution with water, and this was separated by filtration. The acid which remained in solution was extracted with ether, and this was combined with an ether solution of the previously filtered solid and washed several times with water to remove HCl, H_2S

(11) Calaway, (Unpublished Thesis), Georgia School of Technology, 1933.

and any other water soluble impurities. The solution of the acid in ether was then extracted with just less than the equivalent amount of sodium hydroxide and the aqueous solution evaporated. The sodium thiolbenzoate so obtained was purified by washing repeatedly with ether.

It has been previously reported that the sodium salt is obtained in 80% yield by this method, but in none of the runs made here was the yield better than 55%. In an attempt to discover the cause of this loss, the solution of the acid following acidification was extracted immediately with ether, thus avoiding filtration of the solution and prolonged standing in the air. On standing, the acid is readily oxidized by atmospheric oxygen to the disulfide according to the following equation:

$$2\ C_6H_5COSH + 1/2\ O_2 = C_6H_5COSSCOC_6H_5 + H_2O \quad (IV)$$

The subsequent procedure was carried out without interruption, but in spite of these precautions against loss by oxidation the yield was not materially improved.

Altering the conditions of the reaction in subsequent runs was also found to have little effect. The reaction was carried out in the cold, and was also modified by dissolving the sodium sulfide in the water-acetone mixture directly, as originally suggested by Calaway, thereby preventing completely the separation of the solvent mixture and minimizing the possibility of hydrolysis of the benzoyl chloride. In every case the red oil observed by Holder in the ether washings from the purification of the salt was obtained in considerable

amounts. This was found by him to be a mixture of several components, among them benzoyl disulfide, thiolbenzoic acid and benzoic acid. It appears, therefore, that the loss in yield of the sodium thiolbenzoate was due mainly to oxidation of the acid during the reaction and possibly to incomplete extraction of the ethereal solution of the acid with sodium hydroxide.

HEXYL THIOLBENZOATE

In an attempt to synthesize the hexyl ester 20 grams of sodium thiolbenzoate, prepared as previously described, were dissolved in 600 cc. of 95% ethyl alcohol. 16.5 grams of hexyl bromide ($C_6H_{13}Br$) were added and the mixture refluxed for about 14 hours. At the end of this time the alcohol was removed by distillation, leaving sodium bromide, excess sodium thiolbenzoate, and a small amount of oil as the residue. The oil was extracted by washing thoroughly with ether, the ether removed and the residual liquid subjected to distillation under reduced pressure. At fourteen mm. a fraction boiling at 183-184° was collected, and this was redistilled at twelve mm., from which a slightly yellow liquid boiling at 150-151° was obtained. A third distillation at nine mm. gave 3.5 grams of a colorless product which came over at 134-135°.

Elementary analysis of this liquid, which was thought to be the ester, showed that no sulfur was present and therefore could not be the compound sought. It was thought that the ester may have been lost during the distillations. In the first two distillations under reduced pressure, a pressure balance was not available; hence it was impossible to maintain an exactly constant pressure over the period required for the distillation. In view of the later experience with the purification of heptyl thiolbenzoate, it is thought that the ester in this case may have come over as a small fraction boiling

just above the range of the liquid collected, which, due to the slightly varying pressure escaped notice.

Circumstances made the further investigation of the liquid obtained inadvisable.

HEPTYL THIOLBENZOATE

The preparation of heptyl thiolbenzoate was undertaken by the same reaction of the sodium salt of the acid with the alkyl halide. 37 grams of sodium thiolbenzoate and 29.8 grams of heptyl bromide ($C_7H_{15}Br$) were refluxed in alcoholic solution for about fourteen hours. After the first few hours a white gelatinous mass separated on cooling, which later proved to be principally sodium bromide. When the reaction seemed to be complete, the separated solid was filtered off and the alcohol removed. As the alcohol was removed additional amounts of the sodium bromide separated, and this was filtered off from time to time since it caused bumping during the distillation. When all the alcohol had distilled, the residue was extracted with ether, and the sodium bromide previously removed was thoroughly washed with ether. The combined ethereal solutions were then distilled on the water bath. In addition to the ether, a definite fraction boiling at 77-78° under 743 mm. was obtained. The residual liquid in the distilling flask was then distilled under reduced pressure, using a pressure balance to maintain a constant pressure. When the pressure was lowered to seventeen mm. a solid phase separated which was found to be more sodium bromide. The solid was filtered off and the distillation carried out at six mm. Two fractions were obtained, one boiling at 68-80° and the other over a range from 150-175°. The first

fraction was further separated by distillation into three other fractions boiling at 63-65°, 74-75° and 80-81° at seven mm. The first of these gave evidence of being heptyl bromide. Further separation of the higher boiling fraction from the first distillation above was attempted, but came over again as a single fraction at 155-168° under seven mm. pressure. In order to determine whether a lag in the thermometer was responsible for the wide boiling range, or whether the fraction was a mixture of components, it was again distilled and divided arbitrarily into four fractions. When the index of refraction of each was taken, it was found to increase rather regularly from the lowest to the highest boiling fraction, indicating that at least two components were present. Qualitative analysis showed sulfur present in only the highest fraction, and so this was again distilled using a more efficient column. The colorless liquid distilling at 170-172° under ten mm. pressure was collected as the ester. The yield was quite unsatisfactory, being scarcely more than a gram.

In an effort to prove that the compound was heptyl thiolbenzoate, the index of refraction was observed and the molecular refraction calculated from the Lorenz-Lorentz equation:

$$M_D = \frac{n^2 - 1}{n^2 + 2} \frac{m}{d} \qquad (V)$$

Where M_D = molecular refraction, n = index of refraction, m = molecular weight and d = density. The density was found to be 0.974 at 20° (d_4^{20} = 0.974), and the index of refrac-

tion (n_D^{20}) 1.4980. Using these data in the equation, a value of 71.08 was obtained for the molecular refraction. From the values of Eisenlohr (12) the molecular refraction of heptyl thiolbenzoate should be 70.97. This wide variation would indicate that the compound was not the heptyl ester, or else was impure, but these determinations are open to question since a defect in the refractometer used made it impossible to determine the temperature of the prisms with any certainty when the index of refraction was measured. This was not accepted, therefore, as conclusive proof that the compound was not heptyl thiolbenzoate.

In a further attempt to identify the compound, a carbon and hydrogen analysis was carried out using the simplified procedure with the semi-micro combustion apparatus described by Feiser (13) in which an ordinary analytical balance is used forweighing. Sulfur was also determined, the Parr Bomb method (14) being used.

Calculated for $C_{14}H_{20}OS$: C, 71.13; H, 8.53; S, 13.57.

Found: C, 71.91; H, 8.96; S, 13.93.

For some unknown reason a check analysis for carbon and hydrogen could not be obtained. Out of some 18 or 20 determinations made on known carbons, no two runs checked the theoretical, nor did they check each other. The results were

(12) Gilman, "Organic Chemistry", J. Wiley and Sons, New York, 1938, Vol. II, p. 1739.
(13) Fieser, L. F., "Experiments in Organic Chemistry", D. C. Heath and Co., New York, 1935, p. 350.
(14) Parr, J. Am. Chem. Soc., 30, 768 (1908).

low in every case, and when a much larger amount of oxygen than recommended by Feiser was used to sweep out the apparatus after the combustion the results more nearly approached the theoretical, but did not check it. The same difficult was experienced throughout the whole course of this work. In view of the low results usually obtained, the above analysis would seem to indicate that the sample was somewhat impure, perhaps containing other organic matter. The same might be inferred from the sulfur analysis. The amount of material on hand made further purification impossible, however.

Although the analytical results obtained do not show conclusively that the compound is heptyl thiolbenzoate, they do not furnish grounds for serious doubt and indicate that the compound is the ester sought.

LAURYL THIOLBENZOATE

Lauryl thiolbenzoate was prepared by refluxing 23 grams of sodium thiolbenzoate and 25 grams of lauryl bromide ($C_{12}H_{25}Br$) in alcoholic solution for sixteen hours. At the end of this time crystals were observed in the reaction mixture on cooling to about 18°, but these disappeared at room temperature. The excess sodium thiolbenzoate and some sodium bromide formed by the reaction were filtered off and the alcoholic solution cooled in an ice bath. A solid which proved to be the ester separated in glistening white crystals, and these were removed by filtration. As much as possible of the ester was removed in this manner, and the filtrate was then distilled to remove the alcohol, leaving sodium bromide and a red oil as the residue. On cooling, a part of the oil solidified to light red crystals, and so the entire residue was extracted with ether, the ether removed and more of the ester obtained from the residue on cooling. This was filtered off and washed with ether until the crystals were white, and combined with the ester previously isolated. When the ether had been removed from the filtrate a small amount of red oil remained.

The white crystalline ester was recrystallized from alcohol until it had a constant melting point of 34.9-35°. The yield of the purified product was again unsatisfactory, being only 2.2 grams.

The red oil obtained from the reaction was fractionated under

reduced pressure, and at eight mm. three fractions were obtained. The first boiled at 123.5 - 126° and appeared to be lauryl bromide. The second came over at 134-136° and the last was a light red liquid boiling over a range of 170-210°. Time did not permit the further separation and identification of these last fractions.

The identification of the ester was attempted first by means of molecular weight determination. The method of Rast (15) was used and a mean value from three determinations gave a molecular weight of 309.4, which compared favorably with the theoretical value of 306.3.

Carbon and hydrogen analysis by the semi-micro method of Fieser was again unsatisfactory, and as a last resort a sample of the ester was sent to another laboratory for analysis (16). Sulfur was determined by the Parr Bomb method.

Calculated for $C_{19}H_{30}OS$: C, 74.43; H, 9.87; S, 10.47.

Found: C, 73.81; H, 10.93; S, 10.16.

These results indicate that the compound was not entirely free from inorganic impurities, probably sodium bromide. The sample was also evidently not dry, although it was dried in a vacuum dessicator before analysis.

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(15) Rast, Ber., 55, 1051, 3727 (1922).

(16) Carbon and hydrogen analysis performed by Arlington Laboratories, Third and Bryan Sts., N., Arlington, Va.

MYRISTYL THIOLBENZOATE

An excess of sodium thiolbenzoate (25 grams) and 27.7 grams of myristyl bromide ($C_{14}H_{29}Br$) were refluxed in ethyl alcohol for 22 hours. The bromide was not completely soluble in the cold alcohol, but dissolved on heating. At the end of the refluxing needle-like crystals separated on cooling to about room temperature, but dissolved when warmed slightly. The excess sodium thiolbenzoate and some of the sodium bromide were filtered from the reaction mixture, and as much as possible of the ester was removed by cooling in the ice bath and filtering. The alcohol was distilled off from the filtrate, and left sodium bromide and a light brown liquid as the residue. The liquid was taken up in ether solution, which on evaporation to remove the solvent and cooling produced a white solid and a light brown oil. The solid, when filtered, had a very low melting point (26-27°) and readily changed to the liquid state on standing in the laboratory. Time was not available for the identification of these substances.

The ester was recrystallized from ethyl alcohol to a constant melting point of 45.1°. About one gram of fine white crystals was so obtained.

Molecular weight determination was again employed first for the identification of the compound as myristyl thiolbenzoate. A mean value of three determinations made by the method of Rast gave a value of 341.6 as compared with the theoretical value

of 334.3. Carbon was again low when the semi-micro analysis was made, and the results for hydrogen indicate that the sample was not thoroughly dry. Prolonged drying in the vacuum dessicator did not improve the result, however, by any significant amount.

Calculated for $C_{21}H_{34}OS$: C, 75.38; H, 10.25; S, 9.59.

Found: C, 73.16; H, 11.03; S, 9.34.

Although results of the analysis are again not conclusive for myristyl thiolbenzoate, they seem to indicate that the compound is the ester sought.

SUMMARY

I. Three of the higher esters of thiolbenzoate not previously reported have been prepared by the action of the sodium salt of the acid with the alkyl halide. Heptyl thiolbenzoate has been found to be a liquid, and lauryl and myristyl thiolbenzoate have been found to be low-melting solids.

II. Although analytical results for the compounds are somewhat inconclusive, there seems to be little doubt that they are the heptyl, lauryl, and myristyl esters.

III. The reaction used for the preparation of these compounds gives a very low yield, and appears to be rather unsatisfactory as a means of preparation of the higher esters.